REMARKS

After amendment, claims 1-40 and 45-47 remain pending in the present application. Claims 41-44 were previously cancelled. The claims previously have been amended to place the application in condition for allowance based upon the unexpected activity of DOT in inhibiting drug resistant forms of HIV. Support for the amendments to the claims can be found throughout the original specification, including the examples and originally filed claims. No new matter has been added by way of the present amendment.

The Examiner has withdrawn a number of objections and rejections of the instant application. The Examiner has also rejected the previously pending claims for the reasons which are set forth in the August 2007 office action on pages 3-10. Applicants shall address each of the Examiner's concerns in the sections which are presented hereinbelow. It is respectfully submitted that the application after amendment, is in condition for allowance.

The 35 U.S.C. §102 Rejection

The Examiner has maintained the rejection of claims 23-29 and 47 under 35 U.S.C. §102 over Belleau, et al., U.S. patent no. 7,119,202 ("Belleau"), for the reasons which are stated in the office action on pages 3-4. Applicants respectfully traverse the Examiner's rejection.

The claims of the present invention are directed to the use of DOT or its prodrug for the treatment of a drug-resistant form of HIV in a patient. Belleau does not disclose the treatment of a drug-resistant form of HIV utilizing DOT or its prodrug analog. It is noted that Belleau does not even mention drug-resistant forms of HIV and certainly do not disclose DOT or its prodrug analogs for treatment of same. An electronic search of the Belleau patent documents show that the specification does not disclose or suggest the

use of the compounds disclosed therein with drug-resistant forms of HIV. Such a disclosure is nowhere to be found in the cited patent documents.

Moreover, Belleau provides absolutely no biological studies or activity from which one of ordinary skill could glean that DOT was an agent which could be used effectively to treat HIV strains which are resistant to 3TC and/or AZT either alone or in combination with an additional anti-HIV compound as claimed.

Belleau does not any biological data whatsoever and doesn't even mention drug resistant forms of HIV. Without any additional disclosure, it is respectfully submitted that the Examiner has not made out a cogent case that the presently claimed invention is anticipated by Belleau. Noted also is the rather detailed biological data in the present specification (see tables 1-5 on pages 17-20) which clearly evidence that compounds (DOT or prodrug forms) which are disclosed herein exhibit activity against drug resistant forms of HIV, including multiple drug resistant forms and that the compounds which are disclosed and claimed herein represent a viable therapeutic approach, alone or preferably in combination with another anti-HIV agent which exhibits inhibition of HIV by a mechanism other than that of DOT. In essence, the present invention represents a clear advance in the art of treating HIV infections.

For the above reasons, it is respectfully submitted that the claims of the present application are not anticipated by Belleau.

The 35 U.S.C. §103 Rejection

The Examiner has rejected the previously filed claims under §103 as set forth in the office action on pages 4-6 as being obvious/unpatentable over Liotta, Belleau or Liotta and the Merck Manual of Diagnosis and Therapy, 17th edition ("Merck") for the reasons which are set forth therein. For the reasons which are presented below, Applicants respectfully submit that the presently pending claims are non-obvious and patentable over the cited art.

The present invention is directed to methods of o compositions for use in treating drug resistant (primarily 3TC and/or AZT drug resistant) forms of HIV using the claimed compounds (DOT or a prodrug form of DOT) alone or preferably in combination with another anti-HIV agent. Thus, the present invention is directed to the unexpected activity of DOT or its analogs in exhibiting significant inhibition of various drug resistant strains of HIV. The aforementioned biological activity is presented in the specification of the present application in tables 1-5 on pages 17-20. The Examiner rejected the previously pending claims as being obvious over the cited art. Applicants respectfully submit that the instant claims are non-obvious over that art.

It is noted here that the references upon which the Examiner has relied for making his obviousness rejection provide insufficient teachings for providing a cogent argument that the present invention is obvious and consequently, unpatentable. Moreover, those references, Liotta and Belleau were filed 17 (seventeen) and 19 (nineteen) years ago respectively. To date, despite the Examiner's reliance on these references as teaching the present invention, there is no evidence that the basic thymine analog which is claimed herein has been utilized as an effective analog for the treatment of HIV. The present invention is non-obvious over the disclosed teachings.

In the first instance, the Examiner has rejected claims 2-4, 13-16, 31-34 and 45-47 as being unpatentable over the disclosure of Liotta. It is the Examiner's view that because Liotta teaches treating HIV infections generally. it would be obvious to use DOT or its analogs to treat drug-resistant forms of HIV. Applicants respectfully traverse the Examiner's rejection.

Prior to the disclosure in the present application, the art did not recognize, nor could one of ordinary skill predict that DOT or a related analog as claimed would be particularly effective in treating HIV which was resistant primarily to 3TC and/or AZT. That was simply unknown and unknowable unless someone took the time to test DOT against a number of drug resistant strains of HIV. Not only did Liotta *not* test the

disclosed compounds against drug resistant strains of HIV, Liotta does not even mention drug resistant forms in the specification. Given the absence of disclosure to that effect in Liotta, it simply cannot be said with any measure of conviction that the present claims are obvious over Liotta. Liotta only provides evidence of the *somewhat* marginal *in vitro* activity of DOT against HIV (See Table 1, column 17 of Liotta). Without adequate testing, one cannot simply draw any conclusion with respect to the activity of a drug against a drug-resistant viral strain. It is simply untenable to suggest that Liotta somehow renders the present invention obvious.

It is noted that the *in vitro* activity against HIV of compounds which are used in the present invention is shown to somewhat marginal in Liotta (10-20 fold lower activity than other compounds tested). This limited activity against HIV may explain why, a number of years after the basic application for Liotta was filed (in 1991), and until the filing of the present application, DOT was not viewed as a clinically relevant compound for the treatment of HIV. Because of the work by the present inventors, DOT is now viewed as a potentially viable treatment for drug resistant forms of HIV and clinical work is ongoing to provide pharmacokinetic data and additional clinical data to provide DOT as clinically relevant therapeutic agent.

Turning to the rejection or claims 2-4, 13-16, 31-34 and 45-47 as being obvious over Belleau, it is respectfully submitted that the disclosure of Belleau does not in any way render the present invention obvious for the same reasons Liotta does not render the present invention obvious. Belleau is directed to a number of nucleoside analogs, a number of which are posited as being active against HIV. Belleau provides absolutely no biological activity against HIV using DOT or a prodrug form. Belleau does not suggest nor even mention drug resistant forms of HIV or that DOT may be a useful agent against same. Belleau provides absolutely no motivation to provide the present invention. Without providing any biological activity against HIV and without suggesting the use of DOT or a related analog as claimed against a drug resistant form of HIV or even mentioning a drug resistant form of HIV, it is respectfully submitted that one of ordinary

skill in the art could not possibly have recognized the present invention from the disclosure of Belleau.

Further noted herein is the fact that Belleau provides no evidence of efficacy of DOT, and, as in the case of Liotta, no attempt has made to establish the clinical relevance of DOT by the inventors of Belleau or Liotta. Indeed, the activities of the present inventors are the first concerted effort to establish the clinical relevance of DOT as a treatment for drug resistant forms of HIV, an important therapeutic subclass. The present invention is clearly patentable over Belleau.

We now turn to the Examiner's rejection of claims 5-7, 17, 18, 23-29, 35 and 36 as being patentable over Liotta, in view of Merck. Applicants have reviewed the disclosure of Liotta in view of Merck and the Examiner's discussion on pages 9-11 of the August 2007 office action and conclude that the present invention is patentable over the combined disclosures of those cited references.

For the reasons which have been detailed hereinabove, it is respectfully submitted that Liotta fails to suggest the present invention. In fact, Liotta does not even mention drug resistant forms of HIV, let alone their treatment with the claimed compounds. The disclosure of DOT and its putatively somewhat marginal *in vitro* activity as tested, would teach the routineer away from using DOT as an anti-HIV compound. No further development would ensue from a reading of Liotta. Indeed, this is precisely what happened, inasmuch as the teachings of Liotta gave rise to complete activity by the inventors in establishing the therapeutic relevance of DOT against HIV. Turning to Merck, this reference, generic in nature, does not in any way obviate the deficient disclosure of Liotta inasmuch as Merck also fails to suggest that the nucleoside compounds of the present invention may be used to treat drug resistant forms of HIV and in particular, 3TC and/or AZT resistant strains of HIV. Without so much as an oblique mention of drug resistant forms of HIV, the Examiner has concluded that Liotta in view of Merck can be combined to teach combination therapy using DOT or a related compound to treat specific drug resistant forms of HIV. Without so much as even an

oblique reference to same, it is respectfully submitted that the present invention is non-obvious over the combined teachings of Liotta and Merck, especially given the *years of inactivity* by the inventors of Liotta and Belleau in failing to establish the clinical relevance of DOT in treating HIV infections.

Thus, where, as *here,* the prior art is absolutely silent on both the teaching and/or the suggestion of the claimed invention, patentability is instilled. This is especially true where the conduct of the inventors is such that there is a complete failure *for years* to establish an interpretation of the teachings upon which Examiner relies in making the art rejection. It is respectfully submitted that the instant claims are now fully compliance with the requirements of 35 U.S.C.

For all of the above reasons, it is respectfully submitted that the claims are patentable. Consequently, it is respectfully submitted that the pending claims are in condition for allowance and such action is earnestly solicited.

No fee is due for the presentation of the present amendment/response. A petition for an extension of time of two months is enclosed as is a request to debit deposit account 04-0838. Small entity status applies to the present application. A Notice of Appeal is also enclosed as is the request to debit the above-referenced deposit account. Please charge any additional fee due or credit any overpayment previously made to Deposit Account No. 04-0838.

Respectfully submitted,

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Henry D. Coleman
Reg. No. 32,559
714 Colorado Avenue
Bridgeport, Connecticut 06605
(203) 366-3560

Certificate of Facsimile Transmission

I hereby certify that this correspondence is being sent by facsimile transmission to Examiner Olson in Group Art Unit 1623 of the United States Patent Office in Alexandria, VA on January 15, 2008.

Henry D. Coleman, Reg. No. 32,559